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Editorial

Malaria Vaccine Development: A Step Towards Reality

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Malaria, a protozoan parasitic disease caused by five species of Plasmodium i.e., *P. vivax, P. falciparum, P. malariae, P. ovale* and *P. knowlesi* in humans. Nearly half of the world's population, an estimated 3.3 billion people in 97 countries and territories are at risk of malaria infection and 1.2 billon are at high risk (> 1 case of malaria per 1000 population each year) [1]. According to world malaria report 2014, 198 million cases of malaria occurred globally in 2013 (uncertainty range 124-283 million) and the disease led to 584,000 deaths (uncertainty range 367,000-755,000) [1]. Among five species of *Plasmodium*, the most dangerous *P. falciparum* malaria remains the commonest cause of under-five mortality in several countries [2].

There are many effective interventions available against malarial infection. These includes; prevention through mosquito vector control using long-lasting insecticidal bed nets, indoor residual spraying with insecticides, seasonal malaria chemoprevention, intermittent preventive treatment for infants and during pregnancy, prompt diagnostic testing and treatment of confirmed cases with effective combinations of anti-malarial medicines [3]. These measures have lowered the malaria disease burden in many countries. The malaria vaccine is being considered as a complementary intervention, i.e., it could be deployed in addition to fully scaled-up access to and use of non-vaccine malaria preventive measures, prompt diagnostic testing and effective anti-malarial medicines. Over 20 subunit vaccine constructs are currently being evaluated in clinical trials or are in advanced preclinical development. There is currently no commercially available malaria vaccine, despite more than four decades of intense research and development.

The malaria vaccine RTS, S/AS01 is the most advanced recombinant protein candidate that targets the *P. falciparum* at the pre-erythrocytic stage. The clinical testing of RTS, S is at least 5-10 years ahead of other candidate malaria vaccines. This vaccine RTS, S/AS01 is based on the hepatitis B surface antigen virus-like particle (VLP) platform, genetically engineered to include the carboxy terminus (amino acids 207-395) of the *P. falciparum* circumsporozoite (CS) antigen containing B-cell and T-cell epitopes [4]. The hybrid malaria-hepatitis B VLP is lyophilized and undergoes point-of-use reconstitution with GlaxoSmithKline's proprietary AS1 (adjuvant series) consists of liquid suspension of liposomes with two immunostimulant components, 3'-o-desacyl-4-aminophosphoryl lipid A (MPL) and QS 21 (highly purified fractions of saponin derivative isolated from Quil-A, an extract of plant Quillaja saponaria) [5].

Recently in April 2015, the final results of a phase-3 double blind, individually randomised, controlled trial demonstrating the efficacy and safety of RTS, S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa has been published [6]. This vaccine has been developed through a partnership between GlaxoSmithKline Biologicals (GSK) and the PATH Malaria Vaccine Initiative (MVI) with funds from the Bill and Melinda Gates Foundation to MVI. Between March 27, 2009 and January 31, 2014, the study was conducted in 11 centres in seven countries namely Burkina Faso, Ghana, Kenya, Gabon, Malawi, Mozambique and the United Republic of Tanzania in sub-Saharan Africa that were situated in areas with different intensities of malaria transmission. 8922 children (5-17 months) and 6537 young infants (6-12 weeks) were enrolled and included in modified intention-to-treat analyses; of these, 6918 (78%) children and 5997 (92%) young infants were included in the per-protocol analyses. Vaccine efficacy against clinical malaria in 5-17 months old children who received three doses plus a booster on a 0, 1, 2, 20 month schedule was 36% over the full duration of the trial. With a booster of the vaccine the overall efficacy for severe malaria in 5-17 month old children was 32% with reduction in severe malaria, malaria hospitalizations and all-cause hospitalizations. Without a booster dose, no protection was seen against severe malaria, as cases averted in the first 18 months

were shifted to older age groups as efficacy wanes. These results highlight the importance of a booster dose with this vaccine, as efficacy is short lived. Vaccine efficacy against clinical malaria in 6-12 week old young infants who received three doses plus a booster on a 0, 1, 2, 20 month schedule was 18% over the full duration of the trial, with the group that received a booster at 20 months reporting efficacy of 26%. In 6-12 week old young infants, the overall efficacy against severe malaria was not significantly above zero with or without a booster. Lower immune responses are induced by the vaccine in young infants aged 6-12 weeks compared to children aged 5-17 months. The reasons for the difference may be due to co-administration with DTP-containing vaccines and the presence of maternally acquired antibodies to malaria in 6-12 week old young infants. The final results interpreted as RTS, S/AS01 prevented a substantial number of cases of clinical malaria over a 3 to 4 years period in children and young infants when administered with or without a booster dose. Efficacy was enhanced by the administration of a booster dose in both age categories.

This study is currently under review for scientific evaluation by the European Medicines Agency (EMA). If a positive scientific opinion on RTS, S/AS01 is obtained from the committee for medicine products for human use (CHMP) through the European Medicines Agency (EMA) and the vaccine is prequalified by World Health Organization (WHO), malaria endemic countries will need to decide whether to license and use RTS, S/AS01. If licensed in African countries, this vaccine has the potential to make a substantial contribution to malaria control programmes when used in combination with other effective control measures, especially in areas of high transmission [6].

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